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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARTIN ELHAY, CHRISTOPHER C. BRODER, and JIN-AN HUANG

Appeal 2018-004114
Application 14/117,516[1]
Technology Center 1600

Before DEMETRA J. MILLS, JEFFREY N. FREDMAN, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of producing a protective immune response against a Hendra and/or Nipah virus in a horse or pig. The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a).

We affirm.

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[1] According to Appellants, the real parties in interest are The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. ("HJF") and Zoetis Services, LLC. App. Br. 1.

STATEMENT OF THE CASE

The Specification discloses that "HeV [Hendra virus] is . . . known to cause fatalities in human and animals and is genetically and immunologically closely related to NiV ['Nipah virus']." Spec. ¶ 2. According to the Specification, there are "presently no vaccines or therapeutics for prevention of infection or disease caused by Nipah virus or Hendra virus." *Id.* "Thus, there is a need for Nipah virus or Hendra virus vaccines and diagnostics that allow for high throughput production of vaccines and/or diagnostics." *Id.*

The Specification addresses this need, disclosing "an immunogenic composition comprising Hendra and/or Nipah virus G protein, an immunostimulatory complex (ISC) and one or more excipients in an amount effective to elicit production of neutralizing antibodies against the Hendra and/or Nipah virus following administration to a subject." *Id.* ¶ 6. "In some embodiments, the immunogenic composition comprises a saponin, a phospholipid, and a steroid." *Id.*

Claims 16–24, 27, and 28 are on appeal. Claim 16 is illustrative and reads as follows:

> 16. A method of producing a protective immune response against a Hendra and/or Nipah virus in a horse or pig comprising administering to the horse or pig at least one injection of an immunogenic composition comprising Hendra and/or Nipah virus G glycoprotein, wherein the at least one injection contains about 5 μg to about 100 μg of Hendra virus G glycoprotein or Nipah virus G glycoprotein, and an immunostimulatory complex (ISC) comprising a saponin and a sterol, to produce the protective immune response against the Hendra and/or Nipah virus following administration to the horse or pig.

Claim App'x A-2.

The Examiner rejected claims 16–24, 27, and 28 under 35 U.S.C. § 103(a) as being obvious over the combination of Broder[2] as evidenced by Sjölander[3] and McEachern.[4]

FINDINGS OF FACT

1. Broder discloses that in 1994, two Hendra virus outbreaks lead to the death of fifteen horses and two people. Broder ¶ 13.

2. Broder discloses:

> Experimental infections of the horse and pig have been carried out with HeV and NiV respectively and one naturally NiV-infected horse has been examined. The pathology caused by either virus in horses appears to be more severe than that caused by NiV in pigs. In addition to pigs, HeV infection of cats has also been performed and in this case disease resembles that seen in horses, characterized by generalized vascular disease with the most severe effects seen in the lung **(28)**.

Id. ¶ 18.

3. Broder discloses:

> In another aspect of the invention, a soluble HeV or NiV G glycoprotein or combinations thereof are used as a subunit vaccine. The soluble HeV or NiV G glycoprotein or combination thereof may be administered by itself or in combination with an adjuvant. Examples of adjuvants include, but are not limited, aluminum salts, water-in-soil emulsions, oil-in-water emulsions, saponin, QuilA and derivatives, ***iscoms***, liposomes, cytokines including gamma interferon or interleukin 12, DNA, microencapsulation in a solid or semi-solid particle,

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[2] Broder et al., US Patent Publication No. 2009/0041772 A1, published Feb. 12, 2009 ("Broder").
[3] A. Sjölander et al, *Immune Response to ISCOM® Formulations in Animal and Primate Models,* 19 Vaccine 2661–2665 (2001) ("Sjölander").
[4] J. McEachern et al., *A Recombinant Subunit Vaccine Formulation Protects Against Lethal Nipah Virus Challenge in Cats,* 26 Vaccine 3842–3852 (2008) ("McEachern").

> Freunds complete and incomplete adjuvant or active ingredients thereof including muramyl dipeptide and analogues, DEAE dextran/mineral oil, Alhydrogel, Auspharm adjuvant, and Algammulin.

Id. ¶ 96 (emphasis added).

4. Broder discloses:

> [T]he neutralizing antibodies of the invention may be administered as passive immunotherapy to a subject infected with or suspected of being infected with Hendra or Nipah virus. A "subject," includes but is not limited to humans, simians, farm animals, sport animals and pets. Veterinary uses are also encompassed by the invention.

Id. ¶ 88.

5. Broder discloses that "[t]he subunit vaccine comprising soluble HeV or NiV G glycoprotein or combinations thereof can be administered . . . intramuscularly." *Id.* ¶ 97.

6. Broder discloses that "[d]osage and schedule of administration can be determined by methods known in the art." *Id.* ¶ 98.

7. Broder discloses that its compositions may be provided in containers containing "unit doses, bulk packages (e.g., multidose packages) or sub-unit doses." *Id.* ¶ 106.

8. Broder discloses that because the administration of soluble HeV G protein was "able to elicit such a potent immune response with high levels of neutralizing antibodies, it may provide an avenue for vaccine development strategies." *Id.* ¶ 127.

9. Sjölander discloses that "ISCOMs® are a particulate adjuvant system composed of antigen, cholesterol, phospholipid and saponins." Sjölander at 2661.

10. McEachern discloses a study in which "subunit vaccine

formulation containing only recombinant, soluble, attachment glycoprotein from HeV (sG_{HeV}) and CpG adjuvant was evaluated as a potential NiV vaccine in the cat model." McEachern Abstract. In the study:

> Eight adult cats were immunised intramuscularly with vaccine preparations on day 0 and on day 21. Each cat received the same 1 ml dose for both prime and boost injections. All vaccine doses were given via intramuscular injection. Two animals received 50 μg doses (cat 29-50 and cat 30-50), two animals received 25 μg doses (cat 31-25 and cat 32-25), two animals received 5 μg doses (cat 33-5 and cat 34-5) and two animals received adjuvant-alone (cat 27-0 and cat 28-0).

Id. at 2.3. Upon oronasal challenge with Nipah virus, "all vaccinated animals were protected from disease although virus was detected on day 21 post-challenge in one animal." *Id.* at Abstract.

11. Aucouturier[5] discloses:

> Adjuvants play an important role in the efficacy of vaccines as the antigens become more and more purified. Indeed recombinant proteins or synthetic peptides are safer than crude inactivated micro-organism, but less immunogenic. This can be balanced by specific adjuvants. But there is no universal adjuvants and their action is not yet clear and rely on different mechanisms. Then, they must be adapted according to several criteria, like the target species, the antigens, the type of immune response, the route of inoculation, or the duration of immunity.

Auocuturier Abstract.

12. Sanders[6] discloses:

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[5] J. Aucouturier et al., *Adjuvants Designed for Veterinary and Human Vaccines*, 19 Vaccine 2666–2672 (2001) ("Aucouturier"). Aucouturier was cited by Appellants as evidence that the ordinary artisan "would recognize that there is no universal adjuvant." App. Br. 13.

[6] M. Sanders et al., *ISCOM™-Based Vaccines: The Second Decade,* 83 Immunology and Cell Biology, 119–128 (2004) ("Sanders"). Sanders was

> Another important feature of ISCOM™-based vaccines is their ability to induce adaptive immunity in the presence of pre-existing antibody, as is the case in newborns via the acquisition of maternal antibodies. In non-human primates and horses, active immunity was induced in the presence of maternal antibody against measles virus and equine herpes 2 virus, with ISCOM™-based vaccines, but not with conventional killed vaccines.

Sanders at 121.

13. Sanders discloses:

> There are currently two registered ISCOM™-based vaccines for veterinary applications, both for use in horses. The first is an influenza vaccine that has been administered to more than one million horses, with no reports of adverse events. The second, referred to as Equity™ (Pfizer Australia, Melbourne, Australia), is a recently registered novel peptide vaccine to control oestrous behavior in mares and fillies.

Id. at 122.

ANALYSIS

Broder discloses the use of a "soluble HeV or NiV G glycoprotein or combinations thereof . . . as a subunit vaccine," including with an adjuvant such as ISCOM. FF3. In rejecting claim 16 as obvious, the Examiner found that Broder disclosed most of the elements of claim 16. The Examiner acknowledged, however, that Broder did not disclose the administration of about 5 μg to about 100 μg of G protein to horses. Ans. 5. The Examiner also acknowledge that Broder did not disclose the requirement of claim 23 that the first dose be followed by a second dose 21–28 days after the first dose.

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cited by the Examiner in response to Appellants' citation of Aucouturier. Ans. 11; Final Act. (February 13, 2017 Office Action ("Final Act.")) at 7.

The Examiner found that McEachern disclosed the administration of 50 μg per dose to cats "in a prime boost immunization method involving cats with the boosting dose following the priming dose after 21 days." *Id.*

Based on the combined teachings of Broder and McEachern, the Examiner concluded that it would have been obvious to administer Broder's "Hendra or Nipah G protein[] compositions multiple times with 21 to 28 days between the first and second administration and about 5 to about 100 μg of Hendra G protein per dose; and to administer Hendra or Nipah G protein combined with an immunostimulatory complex (ISC) and excipient to horses." *Id.* at 6. The Examiner found motivation to administer to horses in Broder's teaching that they are at risk for infection. *Id.* The Examiner found that the ordinary artisan would have been motivated to administer G protein as claimed because Broder teaches that "compositions that comprise Hendra or Nipah virus G protein, saponin or ISCOMs and an excipient" may be used to "elicit neutralizing antibodies against Hendra or Nipah viruses" and McEachern teach two doses of 5, 25 and 50 μg of G protein, 21 days apart. *Id.*

We agree with the Examiner that claims 16–24, 27, and 28 would have been obvious over cited art. We address the Appellants arguments below.

Claims 16–20, 27 and 28

Appellants argue claims 16–20, 27, and 28 together. We designate claim 16 as representative.

Appellants argue that "neither Broder nor McEachern teaches or suggests a composition having G protein and an ISC composed of a saponin and a sterol" and thus the cited references fail to teach every element of the

claimed method. App. Br. 11. We are not persuaded because Broder expressly teaches that Hendra or Nipah G protein may be combined with an adjuvant, such as ISCOM (FF3) and Sjölander discloses that "ISCOMs® are a particulate adjuvant system composed of antigen, cholesterol, phospholipid and saponins." FF9. Thus, use of an ISCOM adjuvant necessarily includes a saponin and a sterol. FF9.

Appellants argue that "neither Broder nor McEachern administers an immunostimulatory complex to horses" instead "Broder administers G protein, without ISC, to a rabbit and McEachern administers G protein, without ISC, to a cat." App. Br. 12. Accordingly, Appellants contend that the ordinary artisan would not reasonably have expected to "develop a Hendra or Nipah virus vaccine for large animals, such as horses and pigs." *Id.* We are not persuaded.

As discussed above, Broder expressly suggests administering a Hendra or Nipah G protein together with an ISCOM. FF3. The fact that the prior art includes examples in which G protein was administered without an ISCOM does not detract from this teaching. *In re Mills,* 470 F.2d 649, 651 (CCPA 1972) ("[A] reference is not limited to the disclosure of specific working examples."); *In re Chapman,* 357 F.2d 418, 424 (CCPA 1966) ("A reference can be used for all it realistically teaches, and is not limited to the disclosures in its specific illustrative examples.").

As to the claim requirement that the composition be administered to horses or pigs, Appellants do not identify, and we do not find, anything to suggest that Broder and McEchern's teachings regarding G protein vaccines are limited to rabbits and cats. To the contrary, Broder states without limitation to a particular species, that because the administration of soluble

HeV G protein was "able to elicit such a potent immune response with high levels of neutralizing antibodies, it may provide an avenue for vaccine development strategies." FF8. To be fair the "potent immune response" in this statement was generated in rabbits, but Broder does not limit inference drawn from this response – that it may provide an avenue for vaccine development – to rabbits.

Moreover, Broder discloses that Hendra and Nipah viruses can infect horses and that horses have been experimentally infected with Hendra and Nipah viruses. FF1, FF2. And Broder teaches that G protein antibodies can be administered to subjects including "farm animals" and notes that "[v]eterinary uses are also encompassed by the invention." FF4. Horses and pigs are reasonably understood as farm animals. We find that these teachings and McEchern's teaching that administration of a similar HeV G protein composition immunized cats, would have motivated the ordinary artisan to administer Broder's vaccine to horses with a reasonable expectation of success based on the successful administration to rabbits and cats. *See, e.g.,* FF1, FF2, FF4, FF8, FF10.

Appellants acknowledge that there "may be a general disclosure within Broder that an ISC can be used as an adjuvant," but argue that "the record does not establish why one of ordinary skill would have had a specific motivation to choose an ISC from among the many well-known adjuvants listed in Broder." App. Br. 12. Appellants contend that an ordinary artisan would have had no motivation to "pick and choose specific but unconnected portions of McEachern and Broder [to] develop an administration protocol in which an ISC is used as an adjuvant for administration to horses or pigs of a Hev G protein or NiV G protein." *Id.*

Appellants contend that "different adjuvants can affect each animal's immune system in different ways" and thus there would be no expectation that McEachern's "aluminum + CpG" adjuvant would be equivalent to an ISCOM. *Id.* As evidence, Appellants cite Aucouturier as teaching "that one of skill in the art would recognize that there is no universal adjuvant." *Id.* at 13. More specifically, Appellants argue that McEachern would suggest to the ordinary artisan that the positive response reported was "due the presence of the CpG adjuvant and its interaction with the antigen." *Id.* (citing as support, McEachern's statement that "[t]he combination of sGHeV and CpG induced sufficient levels of antigen-specific plasma Ig, neutralising antibodies and antigen-specific mucosal IgA to protect all cats from lethal NiV challenge."). We are not persuaded.

As discussed above, Broder expressly suggests to use an ISCOM as an adjuvant in connection with its soluble HeV or NiV G protein. FF3. We acknowledge that there are no universal adjuvants and an adjuvant must be adapted to, *inter alia*, the target species, route of inoculation, and antigen. FF11. However, given Broder's suggestion to use an ISCOM as an adjuvant in connection with its antigen (FF3), and given that was known to use ISCOMs in horse vaccines (FF12, FF13), we agree with the Examiner that it would have been obvious to use Broder's HeV or NiV G protein together with an ISCOM adjuvant.

Accordingly, we affirm the Examiner's rejection of claim 16. Because they were not argued separately, claims 17–20, 27, and 28 fall with claim 16.

Claim 21

Claim 21 depends from claim 16 and further requires that the "immunogenic composition is administered intramuscularly." Appellants argue that the cited art fails to suggest intramuscular injection. App. Br. 14–15. Appellants contend that "while Broder may contain the word 'intramuscular,' there is no specific direction or guidance in Broder for IM administration to a horse or pig of a composition comprising a HeV G protein or NiV G protein, at a dose of about 5 μg to about 100 μg, with an ISC." App. Br. 14. Appellants similarly contend that "while McEachern administers a composition containing aluminum + CpG to a cat *via* IM, there is no direction to administer an ISC-containing composition *via* IM to any other animal." *Id.* at 15. We are not persuaded.

Both Broder and McEachern expressly disclose intramuscular injection of their compositions. FF5, FF10. We agree with the Examiner that these disclosures are sufficient to render the claimed method of administration obvious. *See,* Ans. 12–13.

Accordingly, we affirm the Examiner's rejection of claim 21.

Claims 22–24

Claim 22 depends from claim 16 and further requires that the "immunogenic composition is administered in multiple doses." Claim 23 depends from claim 22 and further requires that the "first dose is followed be a second dose at least about twenty-one days to about twenty-eight days after the first dose." Claim 24 also depends from claim 22 and further requires that "each dose contains about 5 to about 100 μg of soluble Hendra virus G glycoprotein."

Appellants argue that "[t]he collection of cited references . . . fails to suggest multiple injections of a composition having a HeV G protein or NiV G protein and an ISC to a horse or pig." App. Br. 15. We are not persuaded because Broder discloses packing its compositions in multidose packages and McEachern discloses administration its compositions in two doses. FF7, FF10.

Appellants argue that the claimed dosage amount is non-obvious as applied to a horse or pig. App. Br. 16. We are not persuaded because as discussed above, the teachings of the cited art can reasonably be extended to horses and pigs. With respect to the dosage amount, McEachern teaches dosage amounts of 5, 25, and 50 μg and Broder teaches that dosage "can be determined by methods known in the art." FF6, FF10. Using McEachern as a starting point, it would have been obvious to determine the appropriate dosage for a horse or pig using "methods known in the art" as taught by Broder. FF6. "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

Accordingly, we affirm the Examiner's rejection of claims 22–24.

SUMMARY

For the reasons set forth herein, and those set forth in the Examiner Answer and Final Office Action, we affirm the Examiner's rejection of claims 16–24, 27, and 28 under 35 U.S.C § 103(a) as obvious.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED